PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference HY 3B PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/FI2004/000347	International filing date *(day/month/year)* 07.06.2004	Priority date *(day/month/year)* 06.06.2003

International Patent Classification (IPC) or national classification and IPC
C12P19/34, C12N15/11, C12N7/00

Applicant
RNA-LINE OY et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.04.2005	05.08.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/FI2004/000347

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-30 as originally filed

   Sequence listings part of the description, Pages

   1, 2 as originally filed

   Claims, Numbers

   1-28 received on 12.04.2005 with letter of 06.04.2005

   Drawings, Sheets

   1/2, 2/2 as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☒ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☒ the claims, Nos. 29,30
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/FI2004/000347

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 21-28

because:

☒ the said international application, or the said claims Nos. 21-28 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/FI2004/000347

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13,16,21-28
	No:	Claims	14,15,17-20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-28
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Prior art

Reference is made to the following documents:

D1: WO 01/46396 A (2001-06-28)
D2: JOURNAL OF VIROLOGY, vol. 66, (January 1992), pages 190-196 [XP008034267]
D3: EMBO JOURNAL, vol. 19, (4 January 2000), pages 124-133 [XP002302296]
D4: MOLECULAR CELL, vol. 7, (April 2001), pages 845-854 [XP002302299]
D5: NATURE BIOTECHNOLOGY, vol. 21, (March 2003), pages 324-328 [XP002302300]
D6: PROCEED. OF THE NAT. ACAD. OF SCI. OF USA, vol. 99, (23 July 2002), pages 9942-9947 [XP002277296]

Section III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 21-28 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to novelty, inventive step or the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1. NOVELTY (Art. 33(2) PCT)

V.1.1. In view of the available prior art, a method for mass-production of dsRNA using a RNA virus or replicon having an RNA-dependent RNA polymerase capable of replicating a heterologous nucleic acid target has not been described. The same

applies for a method of inducing sequence-specific gene-silencing using such a virus or RNA replicon. The subject-matter of claims 1-13,16 and 21-28 is therefore new in the sense of Art. 33(2) PCT.

V.1.2. However, a system comprising a virus (especially the ϕ6 bacteriophage) replicating a target nucleic acid (Kan) in a carrier-state cell (*P.syringae*) with extraction of the dsRNA obtained, has been disclosed in D2 and cannot be distinguished from the one claimed in claims 14 and 20. Hence, the subject-matter of claims 14,15,17-20 is not new in the sense of Art. 33(2) PCT.

V.2. INVENTIVE STEP (Art. 33(3) PCT)

V.2.1. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of the claims does not involve an inventive step in the sense of Article 33(3) PCT.

V.2.2. Document D1 is regarded as being the closest prior art and discloses the use of isolated RNA-dependent RNA polymerases (RdRP) from bacteriophages ϕ6 and ϕ14 for the in vitro synthesis of double-stranded RNA, e.g. for use in RNA interference (see the relevant passages as indicated in the ISR). The teaching of D1 clearly indicates an amplification step in the synthesis procedure which allows the obtention of meaningful amounts of dsRNA (see pages 15-23).
A similar teaching can be found in D3.

V.2.3. The subject-matter of the claims (nonewithstanding the objections raised under paragraph V.1. supra) differs from this known teaching in that the replication system is incorporated into a RNA virus or replicon.
The problem to be solved by the present invention may therefore be regarded as an improved system for production of dsRNAs.
The solution proposed in present application cannot be considered as involving an inventive step (Article 33(3) PCT) as from D2 it was already known that bacteriophage ϕ6 is capable of replicating heterologous nucleic acids in carrier state *Pseudomonas syringae* cells (see also D4). Furthermore, production of short interfering RNAs from long dsRNAs by cleavage with ribonucleases such as Dicer

or RNAse III was well known from the prior art as well (see e.g. D5 and D6).

V.3. INDUSTRIAL APPLICABILITY (Art. 33(4) PCT)

V.3.1. The subject-matter of claims 1-20 is considered as being industrially applicable in the sense of Art. 33(4) PCT.

V.3.2. For the assessment of the present claims 21-28 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Item VI. Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
DE10225066	18.12.2003	06.06.2002	06.06.2002

Item VIII. Certain observations on the international application

Attention is drawn to present claims 14-18 which include human (embryos) in their scope. This subject-matter is considered by the EPO as being contrary to morality

(Art. 53 EPC) and corresponding objections will be raised against said claims when entering into the regional phase before the EPO.